III. AMENDMENTS TO CLAIMS

Claims 2-4,10, 16-18, 24, 30-33 and 37, 38 were previously cancelled. Please add new claims 55-69, as set forth below.

IN THE CLAIMS:

1. *(Currently Amended)* A method for screening an individual for colorectal cancer, the method comprising:

a) determining ~~the~~ a total concentration of TIMP-1 in a plasma sample of said individual~~,~~;

b) constructing a percentile plot of total plasma TIMP-1 concentrations obtained from a non-colorectal cancer population;

c) constructing a ROC (receiver operating characteristics) curve based on total plasma TIMP-1 concentrations determined in a non-colorectal cancer population and a colorectal cancer population;

d) selecting a desired sensitivity;

e) determining from the ROC curve the specificity corresponding to the desired sensitivity;

f) determining from the percentile plot the total plasma TIMP-1 concentration value corresponding to the determined specificity; and

g) ~~and~~ indicating the individual as likely to have colorectal cancer if the total concentration of TIMP-1 in the plasma sample of the individual is equal to or higher than said total plasma TIMP-1 concentration value corresponding to the determined specificity ~~is at or beyond a discriminating value~~ and indicating the individual as unlikely to have colorectal cancer if the total concentration of TIMP-1 in the plasma sample of the individual is lower than said total plasma TIMP-1 concentration value corresponding to the determined specificity. ~~is not at or beyond the discriminating value, whereby the~~

~~likelihood that said individual has or will have colorectal cancer is determined, the discriminating value being a value which has been determined by measuring the total concentration of TIMP-1 in both a healthy control population and a population with known colorectal cancer, thereby determining said discriminating value which identifies the colorectal cancer population with a predetermined sensitivity or predetermined specificity.~~

Claims 2-4 (Cancelled).

5. *(Previously Presented)* A method according to claim 41, wherein the combination for the combined parameter and for the total plasma TIMP-1 concentrations with free plasma TIMP-1 concentrations obtained from a non-colorectal cancer population is performed by logistic regression analysis.

6. *(Withdrawn)* A method according to claims 1 or 5, which comprises additionally determining at least one second parameter, the second parameter representing the concentration of an additional tumour marker different from any form of TIMP-1, in a body fluid sample from the individual.

Claim 7 (Cancelled)

8. *(Withdrawn)* A method according to claim 7, wherein the combining is performed by logistic regression analysis.

Claim 9 (Cancelled)

Claim 10 (Cancelled)

11. *(Withdrawn)* A method according to claim 9, wherein the tumour marker is selected from the group consisting of CEA, soluble U-PAR, cathepsin B, HER2-neu, CA15-3 and YKL-40.

12. *(Withdrawn)* A method according to claim 11, wherein the at least one second parameter determined is the concentration of CEA.

13. *(Currently Amended)* A method according to claims 1, 41, 42 or 5, wherein the individual is a member of ~~an unselected~~ a population not already identified as having an increased risk of developing cancer.

14. *(Previously Presented)* A method according to claims 1, 41, 42 or 5, wherein the individual is a member of a population already identified as having an increased risk of developing cancer.

15. *(Currently Amended)* A method for screening an individual, who has been treated for primary breast cancer, for metastatic breast cancer, comprising:

a) determining ~~the~~ a total concentration of TIMP-1 in a plasma sample of said individual,; ~~and indicating the individual as likely to have metastatic breast cancer if the total concentration of TIMP-1 is at or beyond a discriminating value and indicating the individual as unlikely to have metastatic breast cancer if the total concentration of TIMP-1 is not at or beyond the discriminating value, whereby the likelihood that said individual has or will have metastatic breast cancer is determined, the discriminating value being a value which has been determined by measuring the total concentration of TIMP-1 in both a healthy control population and a population with known metastatic breast cancer, thereby determining said discriminating value which identifies the metastatic breast cancer population with a predetermined sensitivity or a predetermined specificity.~~

b) constructing a percentile plot of total plasma TIMP-1 concentrations obtained from a non-metastatic breast cancer population;

c) constructing a ROC (receiver operating characteristics) curve based on total plasma TIMP-1 concentrations determined in a non-metastatic breast cancer population and a metastatic breast cancer population;

d) selecting a desired sensitivity;

e) determining from the ROC curve the specificity corresponding to the desired sensitivity;

f) determining from the percentile plot the total plasma TIMP-1 concentration value corresponding to the determined specificity; and

g) indicating the individual as likely to have metastatic breast cancer if the total concentration of TIMP-1 in the plasma sample of the individual is equal to or higher than said total plasma TIMP-1 concentration value corresponding to the determined specificity and indicating the individual as unlikely to have metastatic breast cancer if the total concentration of TIMP-1 in the plasma sample of the individual is lower than said total plasma TIMP-1 concentration value corresponding to the determined specificity.

Claims 16-18 (Cancelled)

19. *(Currently Amended)* A method according to claim 42, wherein the combination for the combined parameter and for the total plasma TIMP-1 concentration with free plasma TIMP-1 concentration corresponding to the determined specificity is performed by logistic regression analysis.

20. *(Withdrawn)* A method according to claims 15 or 19, which comprises additionally determining at least one second parameter, the second parameter representing the concentration of an additional tumour marker different from any form of TIMP-1, in a body fluid sample from the individual.

Claim 21 (Cancelled).

22. *(Withdrawn)* A method according to claim 21, wherein the combining is performed by logistic regression analysis.

23. *(Withdrawn)* A method according to claim 21, wherein the discriminating value of the combined parameter is a value which has been determined by determining said combined parameter in both a healthy control population and a population with

known metastatic cancer, thereby determining the discriminating value which identifies the metastatic cancer population with a predetermined specificity or a predetermined sensitivity.

Claim 24 (Cancelled).

25. *(Withdrawn)* A method according to claim 20, wherein the tumour marker is selected from the group consisting of CEA, soluble u-PAR, cathepsin B, HER2-neu, CA15-3 and YKL-40.

26. *(Withdrawn)* A method according to claim 25, wherein the at least one second parameter determined is the concentration of CEA.

27. *(Currently Amended)* A method according to claim 15, wherein the determination of the total concentration of TIMP-1 in a plasma sample of said individual is performed at several time points at intervals as part of a monitoring of ~~a cancer~~ the individual ~~patient~~ after the treatment for primary breast cancer.

28. *(Previously Presented)* A method according to claim 1, which detects early stage cancer.

29. *(Original)* A method according to claim 28, wherein the early stage cancer is selected from the group consisting of colon cancer Dukes' stage A, colon cancer Dukes' stage B, colon cancer Dukes' stage C, rectal cancer Dukes' stage A, rectal cancer Dukes' stage B and rectal cancer Dukes' stage C.

Claims 30-33 (Cancelled).

34. *(Currently Amended)* A method according to claims 1 or 15, wherein the determination of the total concentration of TIMP-1 in a plasma sample of the individual is performed by means of an immuno assay or an activity assay.

35. *(Original)* A method according to claim 34, wherein the immuno assay is an ELISA.

36. *(Original)* A method according to claim 34, wherein the activity assay is zymography.

Claim 37-38 (Cancelled).

39. *(Previously Presented)* A method according to claim 1 wherein the colorectal cancer is colon cancer.

40. *(Previously Presented)* A method according to claim 1 wherein the colorectal cancer is rectal cancer.

41. (*Currently Amended)* A method for screening an individual for colorectal cancer, the method comprising:

a) determining ~~the combination of the~~ a total concentration of ~~total~~ TIMP-1 ~~with the concentration of free TIMP-1~~ in a plasma sample of said individual~~,~~ and ~~indicating the individual as likely to have colorectal cancer if the combination of the concentration of total TIMP-1 with the concentration of free TIMP-1 is at or beyond a discriminating value and indicating the individual as unlikely to have colorectal cancer if the combination of the concentration of total TIMP-1 with the concentration of free TIMP-1 is not at or beyond the discriminating value, whereby the likelihood that said individual has or will have colorectal cancer is determined, the discriminating value being a value which has been determined by measuring the combination of the concentration of total TIMP-1 with the concentration of free TIMP-1 in both a healthy control population and a population with known colorectal cancer, thereby determining said discriminating value which identifies the colorectal cancer population with a predetermined sensitivity or a predetermined specificity.~~ a concentration of free TIMP-1 in a plasma sample of said individual;

b) combining the total concentration of TIMP-1 in the plasma sample of the individual and the concentration of free TIMP-1 in the plasma sample of the individual to result in a combined parameter of the individual;

c) determining a total plasma TIMP-1 concentration in a non-colorectal cancer population and a free plasma TIMP-1 concentration in a non-colorectal cancer population;

d) combining the total plasma TIMP-1 concentration of the non-colorectal cancer population with the free plasma TIMP-1 concentration of the non-colorectal cancer population to result in a benchmark combined parameter;

e) constructing a percentile plot of the benchmark combined parameter;

f) constructing a ROC (receiver operating characteristics) curve based on the combination of total plasma TIMP-1 concentrations with free plasma TIMP-1 concentrations determined in a non-colorectal cancer population and a colorectal cancer population;

g) selecting a desired sensitivity;

h) determining from the ROC curve the specificity corresponding to the desired sensitivity;

i) determining from the percentile plot the benchmark combined parameter value corresponding to the determined specificity; and

j) indicating the individual as likely to have colorectal cancer if the combined parameter of the individual is equal to or higher than said benchmark combined parameter value corresponding to the determined specificity and indicating the individual as unlikely to have colorectal cancer if the combined parameter of the individual is lower than said benchmark combined parameter value corresponding to the determined specificity.

42. *(Currently Amended)* A method for screening an individual, who has been treated for primary breast cancer, for metastatic breast cancer, the method comprising:

a) determining ~~the combination of the~~ a total concentration of ~~total~~ TIMP-1 ~~with the concentration of free TIMP-1~~ in a plasma sample of said individual ~~and indicating the individual as likely to have metastatic breast cancer if the combination of the concentration of total TIMP-1 with the concentration of free TIMP-1 is at or beyond a discriminating value and indicating the individual as unlikely to have metastatic breast cancer if the combination of the concentration of total TIMP-1 with the concentration of free TIMP-1 is not at or beyond the discriminating value, whereby the likelihood that said individual has or will have metastatic breast cancer is determined, the discriminating value being a value which has been determined by measuring the combination of the concentration of total TIMP-1 with the concentration of free TIMP-1 in both a healthy control population and a population with known metastatic breast cancer, thereby determining said discriminating value which identifies the metastatic breast cancer population with a predetermined sensitivity or a predetermined specificity.~~ and a concentration of free TIMP-1 in a plasma sample of said individual;

b) combining the total concentration of TIMP-1 in the plasma sample of the individual and the concentration of free TIMP-1 in the plasma sample of the individual to result in a combined parameter of the individual;

c) determining a total plasma TIMP-1 concentration in a non-metastatic breast cancer population and a free plasma TIMP-1 concentration in a non-metastatic breast cancer population;

d) combining the total plasma TIMP-1 concentration of the non-metastatic breast cancer population with the free plasma TIMP-1 concentration of the non-metastatic breast cancer population to result in a benchmark combined parameter;

e) constructing a percentile plot of the benchmark combined parameter;

f) constructing a ROC (receiver operating characteristics) curve based on the combination of total plasma TIMP-1 concentrations with free plasma TIMP-1 concentrations determined in a non-metastatic breast cancer population and a metastatic breast cancer population;

g) selecting a desired sensitivity;

h) determining from the ROC curve the specificity corresponding to the desired sensitivity;

i) determining from the percentile plot the benchmark combined parameter value corresponding to the determined specificity; and

j) indicating the individual as likely to have metastatic breast cancer if the combined parameter of the individual is equal to or higher than said benchmark combined parameter value corresponding to the determined specificity and indicating the individual as unlikely to have metastatic breast cancer if the combined parameter of the individual is lower than said benchmark combined parameter value corresponding to the determined specificity.

43. *(Withdrawn)* A method according to claim 6, wherein the additional tumour marker is a colorectal tumour marker.

Claim 44 (Cancelled).

45. *(Withdrawn)* A method according to claim 44, wherein the combining is performed by logistic regression analysis.

Claim 46 (Cancelled).

47. *(Withdrawn)* A method according to claim 46, wherein the tumour marker is selected from the group consisting of CEA, soluble U-PAR, cathepsin B, HER2-neu, CA15-3 and YKL-40.

48. *(Withdrawn)* A method according to claim 47, wherein the at least one second parameter determined is the concentration of CEA.

49. *(Withdrawn)* A method according to claim 43, wherein the individual is a member of an unselected population.

50. *(Withdrawn)* A method according to claim 43, wherein the individual is a member of a population already identified as having an increased risk of developing cancer.

51. (*Previously Presented*) A method according to claim 14, wherein the individual has a genetic disposition for cancer, has been exposed to carcinogenic substances or has a cancer-predisposing or non-malignant diseases.

52. *(Previously Presented)* A method according to claim 14, wherein the individual is selected from the group consisting of: an individual who had a prior polyp, an individual with Crohn's disease, an individual with an ulcerative colitis, an individual with one or more family members with colorectal cancer, or an individual with a prior resection of early colorectal cancer.

53. *(Withdrawn)* A method according to claim 50, wherein the individual has a genetic disposition for cancer, has been exposed to carcinogenic substances or has a cancer-predisposing or non-malignant diseases.

54. *(Withdrawn)* A method according to claim 50, wherein the individual is selected from the group consisting of: an individual who had a prior polyp, an individual with Crohn's disease, an individual with an ulcerative colitis, an individual with one or more family members with colorectal cancer, or an individual with a resection of early colorectal cancer.

55. *(New)* A method for screening an individual for colorectal cancer, the method comprising:

a) determining a total concentration of TIMP-1 in a plasma sample of said individual;

b) constructing a percentile plot of total plasma TIMP-1 concentrations obtained from a non-colorectal cancer population;

c) selecting a desired specificity;

d) determining from the percentile plot the total plasma TIMP-1 concentration value corresponding to the desired specificity; and

e) indicating the individual as likely to have colorectal cancer if the total concentration of TIMP-1 in the plasma sample of the individual is equal to or higher than said total plasma TIMP-1 concentration value corresponding to the desired specificity and indicating the individual as unlikely to have colorectal cancer if the total concentration of TIMP-1 in the plasma sample of the individual is lower than said total plasma TIMP-1 concentration value corresponding to the desired specificity.

56. *(New)* A method for screening an individual for colorectal cancer, the method comprising:

a) determining a total concentration of TIMP-1 in a plasma sample of said individual and a concentration of free TIMP-1 in a plasma sample of said individual;

b) combining the total concentration of TIMP-1 in the plasma sample of said individual with the concentration of free TIMP-1 in the plasma sample of said individual to result in a combined parameter of the individual;

c) determining a total plasma TIMP-1 concentration in a non-colorectal cancer population and a free plasma TIMP-1 concentration in a non-colorectal cancer population;

d) combining the total plasma TIMP-1 concentration of the non-colorectal cancer population with the free plasma TIMP-1 concentration of the non-colorectal cancer population to result in a benchmark combined parameter;

e) constructing a percentile plot of the benchmark combined parameter;

f) selecting a desired specificity;

g) determining from the percentile plot the benchmark combined parameter value corresponding to the desired specificity; and

h) indicating the individual as likely to have colorectal cancer if the combined parameter of the individual is equal to or higher than said benchmark combined parameter value corresponding to the desired specificity and indicating the individual as unlikely to have colorectal cancer if the combined parameter of the individual is lower than said benchmark combined parameter value corresponding to the desired specificity.

57. *(New)* A method for screening an individual, who has been treated for primary breast cancer, for metastatic breast cancer, the method comprising:

a) determining a total concentration of TIMP-1 in a plasma sample of said individual and a concentration of free TIMP-1 in a plasma sample of said individual;

b) combining the total concentration of TIMP-1 in the plasma sample of said individual and the concentration of free TIMP-1 in the plasma sample of said individual to result in a combined parameter of the individual;

c) determining a total plasma TIMP-1 concentration in a non-metastatic breast cancer population and a free plasma TIMP-1 concentration in a non-metastatic breast cancer population;

d) combining the total plasma TIMP-1 concentration of the non-metastatic breast cancer population with the free plasma TIMP-1 concentration of the non-metastatic breast cancer population to result in a benchmark combined parameter;

e) constructing a percentile plot of the benchmark combined parameter;

f) selecting a desired specificity;

g) determining from the percentile plot the benchmark combined parameter value corresponding to the desired specificity; and

h) indicating the individual as likely to have metastatic breast cancer if the combined parameter of the individual is equal to or higher than said benchmark

combined parameter value corresponding to the desired specificity and indicating the individual as unlikely to have metastatic breast cancer if the combined parameter of the individual is lower than said benchmark combined parameter value corresponding to the desired specificity.

58. *(New)* A method for screening an individual, who has been treated for primary breast cancer, for metastatic breast cancer, comprising:

a) determining a total concentration of TIMP-1 in a plasma sample of said individual;

b) constructing a percentile plot of total plasma TIMP-1 concentrations obtained from a non-metastatic breast cancer population;

c) selecting a desired specificity;

d) determining from the percentile plot the total plasma TIMP-1 concentration value corresponding to the desired specificity; and

e) indicating the individual as likely to have metastatic breast cancer if the total concentration of TIMP-1 in the plasma sample of the individual is equal to or higher than said total plasma TIMP-1 concentration value corresponding to the desired specificity and indicating the individual as unlikely to have metastatic breast cancer if the total concentration of TIMP-1 in the plasma sample of the individual is lower than said total plasma TIMP-1 concentration value corresponding to the desired specificity.

59. *(New)* A method according to claims 1, 15, 41, 42, 56, 57, 58, 60, 61, 62 or 63 wherein the total concentration of TIMP-1 comprises the sum of the TIMP-1 in free form and the TIMP-1 in complex forms.

60. *(New)* A method for screening an individual for colorectal cancer, the method comprising determining a total concentration of TIMP-1 in a plasma sample of said individual, and indicating the individual as likely to have colorectal cancer if the total concentration of TIMP-1 in the plasma sample of the individual is equal to or higher than

the total concentration of TIMP-1 measured in plasma in a non-colorectal cancer population, and indicating the individual as unlikely to have colorectal cancer if the total concentration of TIMP-1 in the plasma sample of the individual is lower than the total concentration of TIMP-1 measured in plasma in a non-colorectal cancer population.

61. *(New)* A method for screening an individual for colorectal cancer, the method comprising:

a) determining a total concentration of TIMP-1 in a plasma sample of said individual and a concentration of free TIMP-1 in a plasma sample of said individual;

b) combining the total concentration of TIMP-1 in the plasma sample of the individual with the concentration of free TIMP-1 in the plasma sample of said individual to result in a combined parameter of the individual;

c) determining a total plasma TIMP-1 concentration in a non-colorectal cancer population and a free plasma TIMP-1 concentration in a non-colorectal cancer population;

d) combining the total plasma TIMP-1 concentration of the non-colorectal cancer population with the free plasma TIMP-1 concentration of the non-colorectal cancer population to result in a benchmark combined parameter;

e) and indicating the individual as likely to have colorectal cancer if the combined parameter of the individual is equal to or higher than the benchmark combined parameter, and indicating the individual as unlikely to have colorectal cancer if the combined parameter of the individual is lower than the benchmark combined parameter.

62. *(New)* A method for screening an individual, who has been treated for primary breast cancer, for metastatic breast cancer, comprising determining a total concentration of TIMP-1 in a plasma sample of said individual, and indicating the individual as likely to have metastatic breast cancer if the total concentration of TIMP-1

in the plasma sample of the individual is equal to or higher than the total concentration of TIMP-1 measured in plasma in a non-metastatic breast cancer population, and indicating the individual as unlikely to have colorectal cancer if the total concentration of TIMP-1 in the plasma sample of the individual is lower than the total concentration of TIMP-1 measured in plasma in a non-metastatic breast cancer population.

63. *(New)* A method for screening an individual who has been treated for primary breast cancer, for metastatic breast cancer, comprising:

a) determining a total concentration of TIMP-1 in a plasma sample of said individual and a concentration of free TIMP-1 in a plasma sample of said individual;

b) combining the total concentration of TIMP-1 in the plasma sample of the individual with the concentration of free TIMP-1 in the plasma sample of said individual to result in a combined parameter of the individual;

c) determining a total plasma TIMP-1 concentration in a non-metastatic breast cancer population and a free plasma TIMP-1 concentration in a non-metastatic breast cancer population;

d) combining the total plasma TIMP-1 concentration of the non-metastatic breast cancer population with the free plasma TIMP-1 concentration of the non-metastatic breast cancer population to result in a benchmark combined parameter;

e) and indicating the individual as likely to have metastatic breast cancer if the combined parameter of the individual is equal to or higher than the benchmark combined parameter, and indicating the individual as unlikely to have metastatic breast cancer if the combined parameter of the individual is lower than the benchmark combined parameter.

64. *(New)* A method according to claim 1, wherein the percentile plot is a plot of the total concentration of TIMP-1 values in a sample of non-colorectal cancer population as a function of specificity.